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Return of the 'last ribo-organism'

SIR—In accusing us of a profound misunderstanding, Maizels and Weiner[1] continue to illustrate the problems encountered as molecular biologists attempt to model the 'RNA world'.

For example, they write that cofactors containing fragments of RNA would emerge in a world of protein catalysts because "nucleotides are far better catalysts than proteins for many reactions". This is wrong. The nucleotide fragments of RNA cofactors are incidental to their chemical reactivities[2]. In the RNA world model, their existence is a 'vestige' of early RNA metabolism[3]. Cofactors that emerged after the breakthrough to the 'protein world', such as biotin[4], are not ubiquitous, lack RNA fragments, and have reactivities reflecting the improved catalytic power of proteins[2-4].

Indeed, Maizels and Weiner's writing is generally confused about vestigiality. If an RNA unit performs a selectable function in the modern world that is intrinsic to the chemistry of RNA and could not be performed as well by proteins, the function is probably not a vestige of the RNA world but has arisen more recently. Therefore, the modern function and intrinsic chemistry of introns and tRNA-like structures at the 3'-terminus of some RNA viruses is evidence against their antiquity, not for it, as Maizels and Weiner write[1,5].

Further, the poly(C)-forming activity of self-splicing introns cannot be viewed as a vestige of "an early RNA replicase"[5]. Drift would have destroyed this activity immediately after it ceased to be functional were it not intrinsically associated with splicing chemistry. And if poly(C)-forming activity is intrinsically associated with splicing, it would be found in self-splicing introns whenever they emerged.

We are agnostics concerning the interesting 'genomic tag' model. But it is weak because it takes an isolated aspect of viral biochemistry and transforms it into a model for the origin of translation in a distant RNA world without a supporting evolutionary tree to place this trait in the progenote (the most recent common ancestor of modern organisms). Moreover, it is quite likely that the trait is adaptive and therefore could have arisen in the modern world, as Maizels and Weiner have acknowledged elsewhere[5].

Maizels and Weiner's disagreement with our focus on a 'breakthrough organism' is less than clear. In the context of the model, there must have been a first organism to contain a genetically encoded message which (given the homology of all modern ribosomes) lived before the progenote. This does not mean, nor have we written, that translation arose "all at once", or that translating and non-translating organisms did not coexist for an arbitrary time. But such a major metabolic innovation must have caused extinctions in a metabolically and ecologically complex RNA world. This means that the breakthrough organism is (at best) the most ancient organism whose metabolism can be reconstructed simply by extrapolation from the biochemistry of modern organisms. Thus, models of the organism, together with prebiotic chemistry, must be the starting points for speculation about the RNA world.

A study of the chemical details of modern metabolism allows us to build these models in some detail[2,6]. For example, deoxyribonucleotides are biosynthesized from ribonucleotides, suggesting that RNA evolved before DNA. However, three (or four) mechanistically distinct ribonucleotide reductases exist in the modern world[7]. In the model, this implies that the breakthrough organism used DNA to store genetic information[8]. This is yet another indication of the metabolic complexity of the last ribo-organism.

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